

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

AEROSOLIZED ANTIBIOTIC THERAPY IN THE ICU

SUMMARY

Aerosolized antibiotics deliver treatment directly to the source of a ventilator-associated pneumonia (VAP). There are currently no large-scale randomized trials evaluating the efficacy of its use. A few small studies provide evidence to support the use of aerosolized antibiotics to treat pneumonia in patients infected with multi-drug resistant (MDR) organisms. This route of administration is especially useful when the minimum inhibitory concentrations for the MDR organism are too high to safely administer intravenous antimicrobial agents. Proper administration technique of the aerosolized antibiotic is needed to ensure optimal distribution and coating of the lungs.

RECOMMENDATIONS

- **Level 1**
 - **None**
- **Level 2**
 - **Nebulizers should create droplet sizes of 1–5 microns for optimal administration**
- **Level 3**
 - **Aerosolized antibiotics may be used in the face of multiple resistant organisms or when intravenous antibiotics may cause deleterious side effects**
 - **All forms of current nebulizers provide adequate administration of antibiotics**
 - **Aerosolized antibiotics should not be administered with humidified air**
 - **Aerosolized antibiotics should be administered with breath actuated nebulizers**
 - **All patients receiving aerosolized antibiotics should be pretreated with aerosolized albuterol 2.5mg prior to each dose**
 - **Specific dosing:**
 - **Amikacin 400 mg aerosolized q 8-12 hrs**
 - **Colistin 150 mg aerosolized q 8-12 hrs**
 - **Gentamicin 80 mg aerosolized q 8 hrs**
 - **Tobramycin (TOBI[®]) 300 mg aerosolized q 12 hrs**
 - **Vancomycin 125 mg aerosolized q 8 hrs**
 - **Each dose should be diluted to a total volume of 4 mL.**

INTRODUCTION

Several attempts at aerosolizing antibiotic therapy were made as early as the 1950's. Antibiotics including penicillin G, ticarcillin, ceftazidime, and carbenicillin were all attempted, but were found to have severe side effects including bronchospasm (1). Other reports showed an increased association with the development of MDR bacteria, atypical bacteria, and increased pulmonary-related mortality (2). These poor outcomes ended research on aerosolized antibiotic therapy for several years, but likely occurred

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

secondary to major methodological shortcomings such as indiscriminate use of antibiotics, the use of antibiotic solution instillation, and treatment of non-ventilated patients (2).

With the development of MDR gram-negative infections such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, the use of aerosolized antimicrobials in the ICU has been restudied. Though aerosolized antimicrobial therapy has been utilized in the cystic fibrosis population for many years, little data exist for the critical care population and the treatment of VAP. Aerosolized antibiotics kill large numbers of bacteria in the tracheobronchial tree and reducing the bacterial load at the source of infection without the need for high serum levels (3-5).

LITERATURE REVIEW

Particle size

Aerosolized antibiotic therapy requires that the medication be nebulized into an airborne molecule. The ultimate determinate of drug deposition into critical portions of the lung requires that the particle be a particular size (6). Unfortunately, nebulizers are unable to produce identical size droplets. Therefore, the mean mass aerodynamic diameter (MMAD) best describes the distribution of the nebulized particle sizes (4,7). This means that 50% of the aerosol mass contains particles smaller than the MMAD while 50% of the aerosol mass is larger. Varying nebulizers will have different MMAD depending on the type and manufacturer.

Ideally, the particle will be one to five microns in size (4,6,7-9). This optimal size is based on the fact that particles that are too small (i.e. < one micron) will likely be quickly exhaled before reaching the lung tissue while large particles (i.e. >five microns) will be too heavy and become trapped on the surface of the endotracheal tube, trachea, and bronchus (6). The use of a slower respiratory rate with higher tidal volume and the use of an end-inspiratory breath hold will increase the likelihood that the particles will deposit on the bronchial mucosa and the location of the pneumonia (7). Also, by using a higher air flow (10 liters per minute), the delivery time can be decreased while at the same time providing appropriately sized molecules (9).

Delivery Devices

There are multiple types of nebulizers currently on the market and amongst these; there is a wide range of variability with as much as a 10-fold difference in the amount of drug delivered. Most nebulizers are designed to deliver a MMAD between 1 – 5 microns. The major factors that influence nebulizers are: mass output, aerosol particle size, composition of inhaled gas, and presence of lung disease (10).

The main two types of devices are the jet nebulizers and ultrasonic nebulizers. Though the two devices are very different, both seem to deliver the solution within therapeutic levels. Eisenberg et al. compared three different nebulizers (1 ultrasonic, 2 jet nebulizers) and found therapeutic levels in >90% of the patients for all nebulizers (11). Minimal systemic drug levels were found in all patients. Miller et al. found that though nebulizers may be similar, there are certain variables that allow optimization of antibiotic administration. Humidifying the air decreases the amount of drug delivered to the patient secondary to water in the air causing the droplets to clump together and more readily attach to the wall of the tubing (5). Breath-actuated nebulization was found to administer a higher dose of antibiotic to the lung than did continuous nebulization (5).

Jet nebulizers

Jet nebulizers force compressed air through a small exit orifice into the ventilator circuit. The air passes by the reservoir of medication and begins to expand after exiting the orifice. This expansion then causes a vacuum that shears the medication away from the reservoir and up into the circuit. Droplets that are too large are blocked by baffles and fall back into the reservoir (4). Interestingly, as the solution is nebulized, the evaporation of the antibiotic causes the solution's temperature to cool down (10). This cooling of the solution coincides with the concentrating of the fluid from evaporative losses and both can affect the nebulizers output and particle size (12,13). Other factors include the solution characteristics, volume, gas pressure, gas flow, and baffle design (4,14-16).

Ultrasonic nebulizers

Ultrasonic nebulizers, through the use of a piezoelectric crystal, generate a vibration which aerosolizes the drug (4,10). Similar to the jet nebulizers, there is a baffle to collect large particles. Unlike jet nebulizers, the particle size may be altered by changing the frequency with particle size being inversely proportional to crystal frequency. The output which is directly proportional to crystal amplitude may likewise be altered. Unfortunately, ultrasonic nebulizers generate heat within the solution which may potentially lead to drug degradation during aerosolization.

Drug Dosing

The data concerning drug dosing is limited to small retrospective studies and case reports as summarized in the attached table. Palmer et.al. have published studies on the use of aerosolized vancomycin and/or gentamicin as well as amikacin for the treatment of ventilator-associated tracheobronchitis (7,8). Tobramycin is the only antimicrobial actually formulated for nebulization and comes pre-packaged in a standard dose of tobramycin 300 mg (17,18,10,20). Colistin (colistimethate sodium or Polymyxin E) has been reviewed in a number of small retrospective studies or case series. Dosing may be expressed as either million units or milligrams. The conversion is approximately 80 mg per 1,000,000 units (10,23-26).

An additional concern with the administration of amikacin, gentamicin, vancomycin, and colistin via nebulization is that the intravenous dosage forms are not buffered and contain preservatives such as phenol and bisulfites (10). The presence of these preservatives as well as the generally hypertonic nature of these antimicrobials contributes to the development of airway irritation, coughing and bronchoconstriction (10). To prevent bronchoconstriction, pretreatment with albuterol is recommended (10).

LITERATURE REVIEW

Palmer et al. conducted a single center, randomized, double-blind, placebo-controlled trial on the use of inhaled vancomycin (120 mg nebulized q 8 hrs), gentamicin (80 mg nebulized q 8 hrs), both, or placebo in critically ill mechanically ventilated patients. The primary endpoint was a reduction in indices of respiratory infection. Secondary outcomes included white blood cell (WBC) count, systemic antibiotic therapy, mortality, and ventilator days. Microbiologic assessments were conducted with weekly tracheal aspirate cultures and also assessed for the development of antimicrobial resistance. Forty-three patients were included (19 in the aerosolized group, 24 in the placebo group). A decrease in the number of patients meeting National Nosocomial Infection Survey criteria for VAP from 73.6% to 35.7% in the treatment group after 14 days of therapy was identified ($p=0.05$). From a microbiologic perspective, there was a significant decrease in the number of resistant organisms isolated on Gram-stain ($p=0.0056$). There was no difference between the groups with regard to WBC before and after therapy or in mortality at 28 days. Fewer patients in the aerosolized antibiotic group required systemic antibiotic initiation during the study as compared to the placebo group ($p=0.042$). There was also no significant difference in the number of patients weaned from mechanical ventilation (12/19 treatment group vs. 13/24 placebo group, $p=0.052$) or in ventilator-free days ($p=0.069$) though when non-surviving patients were removed, weaning from mechanical ventilation was significantly higher in the treatment group (80% vs. 45%, $p=0.046$) (7).

Mohr et al. conducted a retrospective, single center study reviewing patients who received aerosolized antibiotics for the treatment of Gram-negative VAP. Patients received either tobramycin (300 mg nebulized q 12 hrs, N=16) or amikacin (400 mg nebulized q 8 hrs or 1000 mg nebulized q 12 hrs, N=6) based on the organism's susceptibility profile for a mean of 7 days of treatment. No patient developed nephrotoxicity. There was a statistically significant improvement in PaO₂/FiO₂ ratio at the completion of therapy ($p < 0.05$). Twelve of the 26 patients had no further episodes of VAP (17).

Hallal et al. conducted a randomized, placebo-controlled trial using nebulized vs. intravenous tobramycin in 10 mechanically ventilated surgical/trauma ICU patients with documented *P. aeruginosa* or *A. baumannii* VAP on BAL. Patients received either tobramycin (TOBI[®]) 300 mg nebulized q 12 hrs + placebo IV + β -lactam antibiotic IV or placebo nebulized treatment + tobramycin IV q 24 hrs + β -lactam antibiotic IV. Five patients were enrolled in each group; the primary outcome measure was resolution of pneumonia. All patients in the inhaled tobramycin group were cured as compared to 3/5 in the intravenous tobramycin

group. Trends were seen toward lower positive end expiratory pressure (PEEP) and more ventilator-free days in the nebulized group, but did not reach statistical significance. The intravenous tobramycin group showed a non-significant increase in serum creatinine compared to the inhaled tobramycin group (18).

Kwa et al. conducted a retrospective review of patients treated with nebulized colistin for nosocomial pneumonia at their institution. They evaluated 21 patients who received colistin 80 mg nebulized q 6-12hrs for a median of 14 days. Eighteen of the 21 patients met criteria for either clinical cure/improvement and 12 of the 21 patients met criteria for microbiologic cure at the end of therapy. Pneumonia was the cause of death in only 3 of the 10 patients who died. There was no significant change in renal function over the course of therapy for either patient and no symptoms of neurotoxicity were detected. One of the 21 patients developed bronchospasm which resolved with albuterol (25).

Louzon et al. performed a retrospective review of 24 patients treated with a total of 29 courses of nebulized colistin therapy. Twenty-one of the 24 patients were surgical patients. The majority of the patients received colistin 150 mg nebulized q 12 hrs (one patient received q 8 hrs). The majority of the patients had multi-drug resistant *P. aeruginosa*, however, some of the isolates demonstrated resistance to colistin. Overall, the colistin treatments were well tolerated. Three patients developed bronchoconstriction, 5 had symptoms of neurotoxicity, and 8 had changes in renal function (only one progressed to dialysis). Eight of the 29 had microbiologic cure based on subsequent cultures; 11 of the patients had persistently positive cultures and 10 had no follow-up cultures. This study emphasized the importance of verifying antimicrobial susceptibility (27).

Falagas et al. performed a meta-analysis of eight trials comparing the prophylactic administration of aerosolized antibiotics in the ICU. This study, including five randomized studies and three non-randomized studies, had a total of 1,877 patients. Treatment included both aerosolized antibiotics and instillation administered antibiotics. The authors found that ICU-acquired pneumonia was less common in the prophylactic group, but no difference in mortality was noted within the primary analysis of only randomized trials. Within the secondary analysis, which included the three non-randomized trials, the authors found no difference in the incidence of either VAP or mortality. However, fewer patients were noted to be colonized with *P. aeruginosa* and no serious drug toxicities were observed (28). A more recent meta-analysis examined aerosolized antibiotics as monotherapy. The authors identified seven articles for a total of 63 patients. Patients receiving either aerosolized or endotracheally instilled antimicrobial agents had clinical cure rates of 86% and bacteriological eradication of 85%. The authors admitted that the data was limited, but suggested that aerosolized antibiotics were an option in certain cases and hoped the data would encourage clinicians to conduct more studies (29).

Aerosolized Antibiotic Dosing

Study	Type of Study	# of Pts	Age (y)	Major Characteristics	Dose (nebulized)	Duration
Palmer et.al. (2)	Double-blind, randomized, placebo-controlled	43	19-92	ICU, MV	Vanc 120mg/2mL q8 Gent 80mg/2mL q8	Max 14 days
Palmer et.al. (4)	Prospective, serial study, self-controlled	6	19-96	ICU, MV	Gent 80mg q8 Amikacin 400mg q8 Amikacin 400mg q12 (renal failure)	2-3 weeks
Mohr et.al. (8)	Retrospective chart review	22	21-78	ICU, MV	Tobra 300mg q12 Amikacin 400mg q8 Amikacin 400mg q12 Amikacin 1g q12	7-10 days
Davis et.al. (9)	Prospective open-label study	6	52-73	MAC treatment	Amikacin 15mg/kg/day	4-52 months
Hallal et.al. (10)	Randomized, double-blind, double-dummy	10	23-72	ICU, MV, GN VAP	Tobra 300mg q12	14 days
Labiris et.al. (11)	Open-label, single-dose, self-controlled	10	52 ± 21	CF or bronchiectasis	Gent 160mg x1	Single dose trial
Levine et.al. (12)	Prospective, randomized	30	34	Burn pts w/inhalation injury	Gent 80mg q8	10 days
Dhand (7)	Review article	N/A	N/A	N/A	Colistin 40mg q12 Colistin 80mg q12 Colistin 160mg q8 Tobra 300mg q12	Not provided
Hamer (13)	Case series	3	45-67	ICU, pneumonia	Colistin 150mg q12 Colistin 100mg q12	11-14 days
Holloway et.al. (14)	Retrospective chart review	2	15-77	ICU, GN VAP	Colistin 160mg	Not provided
Kwa et.al. (15)	Retrospective chart review	21	61	ICU, MDR VAP	Colistin 80mg q6-12	14 days (2-36 days)
Michalopoulos et.al. (16)	Retrospective chart review	8	60 yrs	MDR VAP	Colistin 40mg q6-8 Colistin 80mg q8 Colistin 120mg q8 Colistin 160mg q8	3-19 days

CF = cystic fibrosis
MDR = multidrug resistant

GN = Gram-negative
MV = mechanical ventilation

ICU = intensive care unit
VAP = ventilator-associated pneumonia

MAC = *Mycoplasma pneumoniae*

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